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EXAMINER	
ARNOLD, ERNST V	

ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,295	RESMAN ET AL.	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,12-18 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12-18 and 20* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 10, 11, and 19 have been cancelled. Claim 20 is new. Claims 1-9, 12-18 and 20 are pending and under examination. The indicated allowability of claims 11-16 in the Office Action filed on 9/12/08 is withdrawn by the present Examiner in view of the newly discovered reference(s) to Ansel et al. (Pharmaceutical Dosage Forms and Drug Delivery Systems 1999). Rejections based on the newly cited reference(s) follow. This Action is non-final.

Withdrawn rejections:

Applicant's amendments and arguments filed 3/6/09 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn. The previous Examiner's rejections are withdrawn. The present Examiner has new rejections.

Claim Objections

Claim 6 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the USPGPUB, [0016] state: "if it is practically insoluble, i.e. less than about 0.1 g/L, in the solvent used." Thus, practically insoluble means less than about 0.1 g/L and therefore is not further limiting to claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating diseases treatable with clarithromycin, does not reasonably provide enablement for *preventing all diseases*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims without an undue amount of experimentation.

Let the Examiner be clear: Applicant is not enabled for *preventing all diseases.*

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: 1) scope or breadth of the claims; 2) nature of the invention; 3) relative level of skill possessed by one of ordinary skill in the art; 4) state of, or the amount of knowledge in, the prior art; 5) level or degree of predictability, or a lack thereof, in the art; 6) amount of guidance or direction provided by the inventor; 7) presence or absence of working examples; and 8) quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure. When the above factors are weighed, it is the

Examiner's position that one skilled in the art could not practice the invention without undue experimentation.

1) Scope or breadth of the claims

The claims are broader in scope than the enabling disclosure. The specification merely discloses, without more, formulations of micronized clarithromycin. However, Applicant is purporting to treat and prevent any and all diseases.

2) Nature of the invention

The nature of the invention is directed to formulation of micronized clarithromycin.

3) Relative level of skill possessed by one of ordinary skill in the art

MPEP 2141.03 states (in part), "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 167 LEd2d 705, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." Id. Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." Id. At 1396, 82 USPQ2d at 1396. The "hypothetical person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art." Ex parte Hiyamizu, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (The Board disagreed with the examiner's definition of one of ordinary skill in the art (a doctorate level engineer or scientist working at least 40 hours per week in semiconductor research or

development), finding that the hypothetical person is not definable by way of credentials, and that the evidence in the application did not support the conclusion that such a person would require a doctorate or equivalent knowledge in science or engineering.). (emphasis added).

4) State of, or the amount of knowledge in, the prior art

The art teaches compositions of micronized clarithromycin (Meyer et al. (US 5609909)).

5) Level or degree of predictability, or a lack thereof, in the art

The art teaches that there is no know way to prevent type 1 diabetes (medical encyclopedia: Type 1 diabetes, page 7 of 7).

The art teaches that there is no known cure for multiple sclerosis (medical encyclopedia: multiple sclerosis, page 3 of 5).

6) Amount of guidance or direction provided by the inventor

Applicant was required to provide in the specification additional guidance and direction with respect to how use the claimed subject matter in order for the application to be enabled with respect to the full scope of the claimed invention. Nothing has been provided about preventing any and all diseases.

7) Presence or absence of working examples

The specification fails to provide scientific data and working embodiments with respect to preventing all diseases.

8) Quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure

One of ordinary skill in the art would have to conduct a myriad number of experiments comprising trial and error administration of the composition to patients with incurable diseases where the consequence of failure can be patient death. Essentially, one of ordinary skill in the art has to figure out how to do this themselves. As a result, one of ordinary skill in the art would be required to conduct an undue amount of experimentation to see if this composition can treat and prevent any and all diseases.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." (Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997)).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 13 recites the limitation "the obtained cores" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claims 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13 recites the limitation "the obtained cores"

and it is unclear what core is intended. Claims 14-16 are rejected as being indefinite because they are based on an indefinite base claim. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 12 states that the active substance comprises particles which are large. The term "large" in claim 12 is a relative term which renders the claim indefinite. The term "large" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. This is also unclear because claim 1 requires that the clarithroymycin be micronized which means the particles are micron sized and therefore not large as compared to a material in the millimeter range. Claims 13 and 14 are rejected as being indefinite because they are dependent on an indefinite base claim. Correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Meyer et al. (US 5609909).

Meyer et al. disclose pharmaceutical compositions comprising micronized clarithromycin in Example 1, column 6:

Example 1

A. Preparation of Clarithromycin: Polyvinylpyrrolidone Particles,

To a pharmaceutically active core consisting of 90% clarithromycin and 10% polyvinylpyrrolidone (Povidone, K-30, ISP Corp), a sufficient amount of food grade ethanol was added with mixing to form a wet mass. The wet granulation was then dried in an oven set at between 50° and 60° C. until the loss of drying (hereinafter referred to as LOD) was less than 1%. These particles were then ground to a smaller size and fractionated using a sieve having a 40–80 mesh. The fraction of particles having a size between 177 and 420 micron was collected.

B. Preparation of Zein-coated Clarithromycin: Polyvinylpyrrolidone Particles.

To 4 kg of clarithromycin: polyvinylpyrrolidone particles, prepared as described above, was applied 2.8 kg of solids contained in a coating formulation consisting of zein (93%) and medium chain triglycerides (7%). This coating formula was dispersed in a mixture of 90% food grade ethanol and 10% distilled water to a level of 10.75% solids (prolamine fraction and medium chain triglycerides), in this cosolvent mixture. The coating was performed in a Glatt GPCG-5 bottom spray particle coater with a fluidized bed and a Wurster column. Inlet temperature was maintained between

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39° and 45° C., with the exhaust temperature between 26° and 29° C., and the atomization pressure on the spray nozzle was maintained between a range of 26 and 30 pounds per square inch. The flow rate of application of the coating liquid to the particles was maintained in the range of 10 to 15 mL per minute. The thickness of the single layer coating is easily varied by adjusting the solids concentrations of the prolamine and hydrophobic plasticizer dissolved in the coating solution.

The use of the composition for the treatment and prevention of disease is inherent in the composition.

Please note that in product-by-process claims, once a product appearing to be substantially identical is found and a 35 U.S.C. 102 rejection is made, the burden shifts to the applicant to show otherwise. This rejection under 35 U.S.C. 102 is proper because the "patentability of a product does not depend on its method of production." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). In addition, please note that the Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether Applicants' pharmaceutical formulation differs and, if so, to what extent, from that of the discussed reference. Therefore, with the showing of the reference, the burden of establishing distinctness is shifted to the Applicants.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a

whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-9, 12-18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Broad et al .US 5705190 in view of Ansel et al. (Pharmaceutical Dosage Forms and Drug Delivery Systems 7th Edition, 1999, Lippincott Williams & Wilkins, NY, pages 91, 108, 209-211 and 221-223).

Applicant claims a method for a physical pre-treatment of an active substance, characterized in that it comprises adding a poor solvent or a mixture of solvents to the active substance or to a mixture of the active substance with [[other]] one or more excipients, the solubility of the substance in said solvent being less than 0.1 g/L, followed by drying, wherein the active substance comprises micronized clarithromycin.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Broad et al. teach sparingly soluble drugs such as clarithromycin (which is intrinsically difficult to be directly tabletted or encapsulated, brittle and/or porous) which has a solubility of about 1 part in 1000 part of water which the Examiner interprets to mean practically insoluble (Abstract; column 1, lines 5-10; column 2, lines 46-59; and column 3, lines 38-40). The amount of drug can vary from about 40 to 75% of the total tablet (column 3, lines 63-65). Dry blending of ingredients followed by wet granulation with an aqueous solution (water is a poor solvent), drying, and tabletting is taught which reads on instant claim 13 (see example 1, column 5, for example). The presence of water intrinsically humidifies the composition. Excipients are taught such as diluents, binders, glidants, bulking agents and coating materials (column 5, lines 1-10). Compositions can be coated (column 5, lines 11-14).

Ansel et al. teach why one of ordinary skill in the art would micronize poorly soluble drugs which is to enhance the rate of dissolution (page 108, right column); how to make tablets through a wet granulation process which introduces water and intrinsically humidifies the ingredients (pages 209-211); teach aqueous film forming coating agents such as hydroxyethyl cellulose and hydroxypropyl methylcellulose (the same material used by applicant: see instant specification page 10, example 5) (page 91, table 3.3; and pages 221-223). Since the agents are the same as instantly claimed then they intrinsically have the same viscosity in the absence of evidence to the contrary.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and Broad et al. is that Broad et al. do not expressly teach micronizing the clarithromycin. This deficiency in Broad et al. is cured by the teachings of Ansel et al.

2. The difference between the instant application and Broad et al. is that Broad et al. do not expressly teach a polymer in the coating with the recited viscosity values or more than one coating agent on a clarithromycin tablet of instant claim 20. This deficiency in Broad et al. is cured by the teachings of Ansel et al.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to micronize the clarithromycin of Broad et al., as suggested by Ansel et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because it is known that clarithromycin is sparingly soluble and Ansel et al. teach that to increase the rate dissolution one of ordinary skill in the art can micronize the drug. This is a common technique in the art of drug formulation.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to add a polymer in the coating of Broad et al. with the

recited viscosity values or more than one coating agent of instant claim 20, as suggested by Ansel et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Broad et al. teach adding a coating and Ansel et al. teach the same polymers to use for the coating. It is merely judicious selection of one or more of the known coating polymers taught by Ansel et al. by one of ordinary skill in the art in the absence of evidence to the contrary. Furthermore, granulation techniques are well known in the art as taught by Ansel et al. and the products can be then film coated as taught by Ansel et al. and discussed above.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (7:15 am-4:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ernst V Arnold/
Examiner, Art Unit 1616